What's New in Tropical Medicine*

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THE term "Tropical Medicine" was many years ago found by its practitioners to be a misnomer. Long search, however, failed to find a better one. Accepting it, then, for its brevity, its emphasis on a major feature, its history and its connotations, tropical medicine means the practice of medicine in warm climates. A warm environment aids the growth of vectors of tropical diseases and of such pathogens as viruses, fungi, bacteria, human protozoa and other parasites, and, very importantly, may alter the quantity and quality of human nutritional agents including caloric values, vitamins, minerals, biologic protein values and their sources. Pathogenic organisms usually occur in luxuriant, perverted or exotic forms in warm climates. As a result tropical medicine differs in emphasis, material and method from the medicine of temperate and cold climates. Human geography, with the geographic influences of climate on man and his artifacts, completes the picture.

In the United States, it is known that many tropical diseases are already present, either endemic (like murine typhus, hookworm disease, trichinosis, amebiasis and malaria), or repeatedly introduced (like dengue). Some, formerly considered rarities of importation, are found more prevalent with better diagnostic methods (as histoplasmosis). Others are minor actualities and enormous potentialities, such as onchocerciasis, leishmaniasis, pinta, yaws, louse typhus, schistosomiasis, American trypanosomiasis and numerous helminths.

Since about 1939, new points of view and research interests in the specialty of tropical medicine, and new factual data in the study and control of specific diseases have appeared or have attained recognition. During this period, these new fields of interest have burgeoned and their importance has been accentuated by increased commercial relations and travel between the United States and more tropical lands, as well as by military necessities. The same applies in a degree to relations between the warmer and the cooler parts of the United States. The emergence of both these conditions found the United States inadequately provided with institutions and men trained in tropical medicine. The advances, foreseen by the few and hitherto ignored by the many, have been unusual.

NEW TRENDS IN TROPICAL MEDICINE IN PAST EIGHT YEARS

War, and the needs of travel and commerce have brought a sharper realization that the world areas of hot wet, and hot dry climates must be studied as a whole for the first time with reference to land utilization and the food supply of the human race.

The teaching of tropical medicine in medical schools has received intensive consideration. Necessary and valuable advances were made in provision of material and trained instructors in practically all medical schools. With the let-up in military requirements, it remains to be seen if the medical schools will provide in the future to a sufficient extent for the practical needs of their students, for the certain needs of the military, of commerce, of travelers and missionaries, and for the requirements of wide fields of preventive medicine. Tropical diseases for the United States are today a sufficient threat to justify medical school instruction in recognition and control. This instruction should be "adequate and required."[1]

The national and world need for research and graduate teaching in tropical medicine have received splendid recognition in the establishment of the Liberian Institute of the American Foundation for Tropical Medicine, Inc. This Institute, in the words of Doctor T. T. Mackie, its president, "represents a partnership between the government of the Republic of Liberia, American business and American science." It will afford a well-equipped field station for intensive study of medical and economic problems of hot climates. Of the new things in tropical medicine, the establishment of the Liberian Institute is one of the most significant.

NEW FACTUAL DATA

New factual data in the study and control of specific diseases have appeared in tremendous number. Among these some of the more important can best be noted under the respective diseases.

Advances in *malariology* have been outstanding, so much so as to raise the hope that world-control of malaria is a possibility.

In chemotherapy[2] Paludrine (N_1-para-chlorophenyl-N_5-isopropyl guanide acetate) has been developed by Fairley,[2] et al. in an extensive research involving 500 human volunteers from the Australian army at Cairns, Australia. Fairley concludes that "paludrine is superior to all known anti-malarial drugs, as, in non-toxic dosage, it is a complete causal prophylactic in falciparum malaria." It shows highly lethal action on pre-erythrocytic forms of *Plasmodium falciparum*, and a single dose of 50 to 100 mg. given orally two to five days after exposure to infective bites, provides complete protection. In *vivax* malaria, paludrine in all cases acts as a partial causal prophylactic but complete eradication of extra-erythrocytic forms does not occur regularly, so that overt attacks are apt to follow discontinuance of the drug. Paludrine quickly controls clinical attacks of falciparum malaria and produces complete cure. In

*Presented as a part of the symposium discussion, "What's New," before the Section on General Medicine at the 76th Annual Session of the California Medical Association, Los Angeles, April 30-May 3, 1947.

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vivax overt attacks, radical cures have not yet been determined. Paludrine does not kill sexual forms in the human carrier but it does sterilize these forms in the mosquitoes fed on human blood containing sexual forms of both *vivax* and *falciparum* as early as one to two hours after the first dose of the drug is taken. This action persists for a variable time until the drug has been eliminated. Paludrine is remarkably free of toxicity, and there is a wide margin between therapeutic and toxic dosage. No example of idiosyncracy to the drug has been seen thus far. In non-immunes a single dose of 100 mg. may terminate a clinical attack in both *falciparum* and *vivax* malaria. In *falciparum* infections it is a true causal prophylactic if given within two to five days after infective bites in a recommended dosage of 100 mg. twice weekly. In *vivax* infections 100 mg. once each week controls relapses indefinitely.

Chloroquine (7 - chloro - 4(- 4 diethyl amino - I methylbutyl amino) quinoline), like paludrine, seems superior to atabrin, in that it causes no gastro-intestinal or cerebral symptoms, and no skin pigmentation; it brings faster disappearance of clinical symptoms; and, in *vivax* infections, relapses are fewer and at longer intervals. Full treatment of an overt attack consists of 600 mg. orally on the first day, followed by 300 mg. on each of the three successive days. For suppression 300 mg. once each week is sufficient.

Pentaquine (6 methoxy-8-(5 isopropyl amino amyl amino)-quinoline) is reported more powerful than quinine or atabrin.[4] Its use in man has been limited almost completely to treatment of *vivax* infections under experimental conditions in the South Pacific. It is too toxic for continued suppressive use. A daily dose of 60 mg. of the base (80 mg. of the di-phosphate) given together with 2.0 grams of quinine in divided doses at four-hour intervals for 14 days, is radically curative in *vivax* infections. The maximal daily dose is 60 mg. It must be given under strict medical supervision, preferably in hospital. Racial toxicities and optimum dosage for children are not yet certain. Pentaquine is equal to plasmochin in activity and half as toxic.

Atabrin has proved to be a successful suppressive in dosage of 100 mg. daily. Overt malarial attacks practically never break through. It can replace quinine except under special conditions. Its continuance for a minimum of one month eliminates practically all *falciparum* infection. Its discontinuance is usually followed by relapses of *vivax* infections. Overt *vivax* attacks are controlled by the standard dosage of 1.0 gram in five divided doses in 30 hours, followed by 100 mg. three times daily for five or six days. The hydrochloride can be used intra-muscularly for the same indications as intravenous quinine. It causes harmless yellow pigmentation of the skin and often gastro-intestinal symptoms which are largely preventible. Suppressive treatment with atabrin requires discipline and training. When it is used constantly, even extreme so-called triggers for overt attacks (such as exhaustion, chilling, etc.) do not break through into clinical attacks of malaria.

An extra-erythrocytic stage of malaria has been demonstrated in six bird malarias, and circumstantially proved in man. This stage follows the quick disappearance of sporozoites after their inoculation by the mosquito and precedes the first appearance of ring-forms in the red cells. Recently it has been postulated that cyclical development in this fixed tissue stage is closely related to persistence of malarial infection and malarial relapses. Sapero [5] says "A prolonged period of fixed tissue development with repeated partial expulsion of parasites would lead to a relapsing disease, and to its termination only when all the parasites are expelled." This is the general situation in *vivax* malaria. Difference between strains of one plasmodial species would cause difference in fixed tissue cycles and in clinical patterns. In therapy, quinine, atabrin and chloroquin act on plasmodial stages in red cells, while plasmochin, paludrine and pentaquine act chiefly on fixed tissue stages. This explains the failure of atabrin to cure *vivax* malaria. This concept is the basis today of malarial therapy.

Entomologic control has been vastly improved by expert technical organization and supervision, and the use of new larvicides and insecticides. Fuller knowledge of mosquito breeding habits has been applied on the basis of local entomologic studies. DDT has permitted effective larvicidal campaigns and also direct destruction of adult mosquitoes in significant quantities. Both are possible with lighter applications of DDT than of older drugs. In adult mosquito destruction, spraying of housing interiors and impregnation of bed nets have been developed effectively. Adult eradication has become a valuable adjunct to mosquito control and of primary value where cost and inaccessibility make larvicidal methods difficult or ineffective. The prolonged residual action of DDT is utilized in aerosols which are at the same time insecticidal and larvicidal.

The spread of new vectors in an area is now well curbed by new spraying methods for planes and ships and control of ports and airfields.

Insect control in general with preparations of DDT and similar substances has made possible the rapid destruction of mosquitoes, flies, lice and other vectors and intermediate hosts. The result is the ability quickly to control the spread of malaria, filariasis, dengue, enteric fevers, sandfly fever, louse typhus, relapsing fever, bartonelliasis, leishmaniasis and other diseases. Soon to be on the market, are *Rhothane*, one-fourth as toxic as DDT for warm-blooded animals and more powerful as a mosquito larvicide, and *Lethane*, a safe and effective household insecticide for mosquitoes, roaches, bedbugs, weevils, clothes moths, flies and fleas.

A new *raticide* has been discovered in sodium fluoro-acetate which is highly lethal to these rodents but is also extremely dangerous for domestic animals and man.

Insect repellents have important additions in di-

methyl phthalate, dibutyl phthalate and benzyl benzoate. These have been used in various emulsions to make clothing resistant to insects and to repel insects from the skin. They are effective for various periods of time against chiggers, mites, mosquitoes, cercariae of schistosoma, and flies. Clothing impregnated with benzyl benzoate, even after several launderings, still repels mites and is lethal for schistosomal cercariae. This drug is an effective treatment for scabies.

Penicillin has proved an efficient treatment for the tropical spirochetoses—yaws, pinta, lepto-spirosis and relapsing fever. It is a valuable alternative when arsenic is contra-indicated. It is used in septic complications of typhus, where sulfa drugs are contra-indicated.

The story of sulfa drugs in *bacillary dysentery* was a dramatic war chapter. Sulfadiazine by preference is highly specific and also has been used in 1.0 gram doses daily as a prophylactic where infection is to be expected.

One striking and highly important discovery has been that para-aminobenzoic acid is a relatively specific remedy in *typhus fever* in the first several days of infection. It has been used in epidemic (louse-borne) typhus, spotted fever and scrub typhus. An initial dose of from 4.0 to 8.0 grams followed by 2.0 grams each two hours practically removes risk of fatality. It is important to give the patient sufficient bicarbonate of soda during the course of treatment to keep the urine neutral. Frequent blood counts should be taken during treatment, also, to make sure that a neutropenia is not developing. A blood plasma level of 30-60 mg. per 100 cc. is necessary. The use of para-amino-benzoic acid strictly contra-indicates the use of sulfa drugs. The Cox type of vaccine (egg yolk sac culture of rickettsia) and the Castaneda mouse lung vaccine have brought a substantial reduction in morbidity and have practically wiped out mortality from epidemic typhus in vaccinated persons. Louse control by DDT dusting of clothing and persons has added greatly to the effectiveness of typhus control. Impregnated clothing furnishes another protection.

In *leishmaniasis* several new drugs are in use. Best among these are *solustibosan* (sodium antimonyl gluconate) and, for the resistant types, *stilbamidine* (4, 4 diamidino stilbene). The latter is more toxic and requires more cautious use.

The therapy of *plague* is finally on a curative basis provided treatment starts on the first day before bacteremia sets in. The drug of choice is sulfadiazine which is given in an initial dose of 4.6 grams, followed by 1 to 2 grams each four hours for ten days or until the fever ends. After this period 0.5 gram should be given each three hours for 14 days after temperature is normal. Fluids and sodium bicarbonate must be adequate with each dose. In fulminating cases, sodium sulfadiazine is given intravenously. In addition anti-plague serum (rabbit or horse) should be given in full doses. Such combined treatment in bubonic plague gives an excellent prognosis. Fatalities are due to delay in starting treatment. Primary pneumonic plague, which is clinically a different disease, is almost always fatal in any case. Even vaccinated plague patients may die if not treated. It is always to be remembered that under natural conditions plague is the most probably fatal of all diseases.

Immunization against plague has resulted in increased attention to vaccination with attenuated or avirulent strains. Jawetz and Meyer [3] consider properly tested live vaccines as safe, and superior in immunogenic power in experimental animals to any killed vaccine available at the time. The Haffkine type of killed vaccine has been improved so that vaccinated persons have four times the protection of the unvaccinated. In Java, South Africa and Madagascar, the Otten type of living avirulent vaccine has given 80-90 per cent protection.

Plague control combining DDT for fleas, sodium fluoro-acetate for rats, vaccination, and early treatment, is highly effective.

Treatment of *cholera* has been put on a new plane by combining sulfadiazine with plasma. Used early, this method practically makes certain the recovery of the patient. The death rate from cholera in India in unvaccinated and untreated persons has been 40-70 per cent. Protection by killed vaccines made from virulent strains of vibrios has been about 90 per cent as compared with the high susceptibility of unvaccinated persons.

Folic acid has opened a new chapter in the cure of sprue and tropical macrocytic anemias.

Leprosy treatment on a definitive basis has been advanced, especially at Carville, by use of several drugs, combined, particularly promine diasone and streptomycin.

Miscellaneous advances have been made in numerous diseases, as examples of which the following may be mentioned. Species-specific methods for immunologic and serologic diagnosis have been greatly improved and made of practical use in louse and rat-borne typhus, scrub typhus, spotted fever, *Q* fever, bartonelliasis, amebiasis, kala azar, espundia, oriental sore and Chagas disease. Improved group-specific antigens have been discovered for the diagnosis of Bancroft's filariasis, onchocerciasis and the schistosomes. Concentration methods have been perfected for micro-filaria and schistosoma ova. It seems likely that effective vaccines will shortly appear for sandfly fever, dengue and scrub typhus.

CONCLUSION

The advances in tropical medicine since 1939 have been highly promising for the control of some of the greatest disease killers of mankind. Future needs and achievements to date make tropical medicine a valid specialty which justifies support in peacetime as it forced support in wartime. Simmons [6] furnishes an excellent review of the wartime contribution of tropical medicine: "This wartime experience with tropical diseases was a severe jolt to the complacency of those who formerly assumed that tropical medicine was

no longer of importance to the United States. It showed that the diseases of the tropics are still a hazard to Americans who travel or live in certain foreign countries. It showed that this country is still exposed to invasion by exotic diseases and indicated the importance of modifying quarantine procedures to meet the new methods of transportation. Finally, it emphasized the urgent need for a continuing program of research and training in order to control tropical diseases, both here in the United States, and in their tropical reservoirs."

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What's New in Cardiovascular Disease*

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PROGRESS in the field of cardiovascular disease during the past year has been delayed, as in other fields, by the readjustment period following the war, but some notable progress has been made. Several reports during the past year suggest that greater advance may be expected in the near future.

SYMPTOMS

Hunter [11] has reported a conspicuous absence of pain in Negroes with coronary artery occlusion, expressing the belief that dyspnea rather than pain is the usual initial symptom in coronary artery closure in this race. Smith [20] has challenged this view vigorously and expresses the opinion that there is no justification for it.

ELECTROCARDIOGRAPHY

The most significant change in this field during the past year is perhaps a general appreciation of the importance of multiple precordial leads in the identification of myocardial infarcts, and the general recognition of the fact that we have been overlooking infarcts in the past by failure to use more than a single precordial lead.

TREATMENT

Subacute bacterial endocarditis: Agreement is now fairly general in regard to the principles of treatment of this disease and has been well expressed by Hunter.[10] Anticoagulant therapy is now regarded as contra-indicated. Identification of the organism, in vitro testing of its sensitivity to antibiotics, and the production of a blood level of drug four to five times that required to kill the organism in vitro are now regarded as fundamentals. Frequent injections of drug as often as every one to two hours are regarded as essential with constant intramuscular drip preferred by some. The minimum period of treatment should probably be three weeks. With adherence to these rules, it should be possible to cure about 90 per cent of the cases.

Salicylates in rheumatic fever: The value of salicylates in rheumatic fever continues to be recognized, but the intravenous route for their administration is no longer considered to offer any advantage over the oral route.[8]

Rice diet in hypertension: Kempner [12] has reported further experience with a diet consisting of rice, fruit, and sugar. Among 222 patients improvement was noted in 62 per cent. Lowering of blood cholesterol levels, reduction in heart size, improvement in the electrocardiogram, and retinal changes were reported.

Low sodium diet in congestive failure: The importance of this diet in mobilization of fluid is becoming generally appreciated to the gratification of patient and doctor alike. A review by Wheeler, Bridges and White, followed by a discussion by Schemm, is to be found in a recent issue of the *Journal of the American Medical Association.*[21]

Dicumarol in acute coronary occlusion: Nichol and Page [14] and Peters, Guyther and Brambel [15] have reported the prevention of emboli, both pulmonary and arterial, following coronary occlusion by the use of this anticoagulant and have indicated that mortality is probably reduced. At the present time, however, the widespread use of the drug in this connection is probably to be discouraged [19] because of the theoretical hazards and expense, and because carefully controlled studies to define the indications and contra-indications of the method are now being carried out by a committee of competent observers appointed last spring by the American Heart Association.

*Presented as a part of the symposium discussion, "What's New," before the Section on General Medicine at the 76th Annual Session of the California Medical Association, Los Angeles, April 30-May 3, 1947.